3. Creatinin showed roughly a proportionate increase.

4. The difference between determined forms of nitrogen and total non-protein nitrogen was greatest in cases with clinically most severe symptoms.

5. In the spinal fluid the increase in nitrogen is almost solely in urea nitrogen except in cases of anuria.

6. We can see no advantage in quantitating the nitrogen of the spinal fluid over quantitating it in the blood.

7. No relationship existed between the amount of non-protein nitrogen in the blood and changes in the retina.

C. DIURESIS IN RELATION TO DIURETICS. 1. Diuresis is relatively infrequent in the average hospital patient.

2. Except for diuresis in cardiac cases following digitalis, diuresis bears an inconstant relation to diuretic drugs.

3. In cases of nephritis with or without edema and without cardiac decompensation, diuretic drugs more often fail to produce a diuresis than the reverse.

4. In cardiorenal cases, diuretic drugs often produce a striking diuresis.

5. Our observations justify a healthy skepticism as to the efficacy of diuretic drugs in cases of nephritis without cardiac decompensation.

D. FUNCTIONAL TESTS IN RELATION TO ANATOMICAL CHANGES IN THE KIDNEY. 1. In 18 cases of chronic nephritis dying and coming to autopsy no constant relations have been found between anatomical lesions and renal function insofar as excretion of phenolsulphonephthalein, albumin in the urine, casts, presence or absence of edema, blood-pressure determinations, etc., are concerned.

STUDIES IN MONILIASIS OF THE DIGESTIVE TRACT IN PORTO RICO.[1]

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IN April, 1913, I wrote a paper[2] for the Tenth Annual Meeting of the American Society of Tropical Medicine, entitled "Notes on Sprue in Porto Rico, and the Results of Treatment by Yellowed Santonin," announcing the presence of that disease in the island. The paper was the outcome of a clinical study of 86 cases extending over some four years. While the disease, under the name of tropical scurvy or intestinal phthisis, has undoubtedly caused a formidable mortality for many years, of late, perhaps in the last decade, it has made startling advances and has now come to occupy a position in the very front rank of the serious and fatal affections of our island, especially dreaded by American residents, among whom it seems to be far more common and fatal than tuberculosis. That it is a disease caused by a specific organism seemed to me likely from the first. The paths most likely to lead to a recognition of that organism seemed: (1) A clinical investigation of the disease, and (2) an epidemiological survey of varied points on the island.

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[1] Read before the Association of American Physicians, May 11, 12 and 13, 1915, in Washington, D. C.

[2] Am. Jour. of Trop. Dis. and Prevent. Med., 1913, I, 146.

Clinical experience with sprue from the early part of 1909, convinced me that, among other things, it was a separate and distinct clinical entity with four cardinal conditions, sore mouth, excessive intestinal fermentation, light, foamy diarrhea and a diminution in the size of the liver; that it was a chronic affection, with periods of relative health; that no specific had yet been found, nor was any medication comparable to a non-carbohydrate diet, santonin having been found wanting after long and persistent use, and discarded in 1913 for emetin, which suffered a like fate. In that year the Institute of Tropical Medicine and Hygiene made their annual expedition to the country districts of the interior and fixed the clinical laboratory, hospital and dispensary in a coffee plantation in the mountains of Utuado. We saw in open clinic for all diseases in a period of sixty working days, 10,140 persons, receiving over 36,000 visits. All physicians working with us were instructed to send cases not uncinariasis, as well as cases suffering from complications of that disease, to our special examining room, and as one of the diseases which we were especially seeking in our medical survey was sprue, it is not probable that many cases of it escaped our vigilance. Only 11 cases of complete sprue and 19 doubtful cases were seen, most of them from the town of Utuado. Thus the fact was disclosed that while occasionally found in the rural districts, sprue was really a disease of towns and cities, preferring to take its victims from the higher walks of life rather than from the less sanitary and apparently more exposed poor. For the purpose of contrast, let us consider 25 as the average minimum number of cases of sprue seen each year by physicians in San Juan who are on the watch for it. In this connection let it be said that among these physicians there is little contention over its tendency to present itself in family endemics.

Previously to this expedition, I had concluded that a likely source of infection was bread, rarely consumed by the country laborer, at best intermittently, and a staple in the home in towns. Porto Rican bread was in 1898–1903 a very savory food. Its peculiarly pleasant taste and European style of confection, accredited it to every table. But the bread of Porto Rico has degenerated much in flavor and in confection in the last ten years, complaints of its sourness and soddenness have become more and more frequent, and coincident with this deterioration intestinal fermentative conditions have increased.

Bahr's[3] "Researches on Sprue" was discouragingly received by some of his colleagues, who replied to his modest statement that the circumstantial evidence pointed to *Monilia albicans* as being the cause of the disease by expressing their inability to accept as a causal agent a fungus common in England where sprue is unknown. At that time I had under my care one of the most typical and, considering the sanitary excellence of his house, one of the most disquieting cases of sprue to American residents which had up to that time claimed public attention. The patient, a young government official, gradually reached the stage of marasmic toxemia, in spite of drugs, trips to the North, and even the classical diet. I sent him North after a partially successful dietetic regime extending over three or four months, and in New York the same diagnosis was independently made by Dr. Crow, U. S. N., who had seen sprue in the East. His return coinciding with the newer ideas of the etiology of sprue, I made three unsuccessful attempts to obtain a growth of yeasts from the denuded but non-inflamed tongue. One day, however, in the midst of an attack of sore tongue, a growth was obtained by scraping, and this culture, together with three others, two of which were cases of tongue sprue in children, formed the basis for a preliminary note[4] entitled "A Monilia Found in Certain Cases of Sprue."

From that time to the present I have made 240 cultures from the tongue, and 50 from the feces in 197 persons, all my own patients and all under my constant observation save five. I divided my sources of culture into three groups: (1) Cases of clinical sprue. (2) Cases with symptoms indicating involvement of the digestive tract, chiefly of a fermentative nature ("gastric and intestinal dyspepsia," etc.), or those presenting a simple stomatitis. The clinical picture of sprue lacked clearness in this group. Herein are included cases entirely cured of a past typical sprue. (3) Cases surely not sprue, and bereft of past or present history of disease of the digestive tract.

The first group consisted of 49 cases; 27 presented a clear picture with the four cardinal symptoms of complete sprue at the time of examination, and an actively inflamed and typical sprue tongue; 20 were cases of the intestinal type at the time cultures were made, but 7 gave histories of having had the complete picture previously; 2 were cases of tongue sprue, but also gave previous histories of the complete type.

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[3] Trans. Soc. Trop. Med. and Hyg., April, 1914, vii, No. 5.

[4] Jour. Am. Med. Assoc., 1915, xiv, 810.

All were promptly positive for monilia. Forty gave the cultural characteristics of the new monilia only and the remaining 9, apparently identical on Sabouraud's glucose agar, have not yet been grown in the required media. This gives a percentage of 100 for this group positive for monilia, all probably identical with the new species.

The second group consists of 82 cases. There are many in which no justification for a suspicion of sprue exists, but they are retained in this group because they give past or present histories of gastro-intestinal disturbance. They may be subdivided as follows: (1) Cases whose histories are suggestive of sprue, and in whom some symptoms still exist. These histories do not, however, justify a positive diagnosis. There are 19 in this subdivision. One gave a positive culture for the new species. Four gave monilias of type entirely distinct from mine, and in 3 of these cases the diagnosis of pellagra was pending. In one of these it has been positively confirmed. Five are frank cases of pellagra now, and all were negative for monilia after repeated search. (2) Cases with a history of gastro-intestinal vagaries in which the dominant note is usually "fermentative dyspepsia." There are 29 in this subdivision: 14 were positive for monilia, 7 for my species and 7 clearly not mine. (3) Cases with inflamed tongue alone. There are three such cases, all negative for monilia. (4) Cases giving a clear history of past sprue generally some years back. There were 20 of these, and all were negative for monilia. (5) Five cases with a colorless history, or a history not diagnostic of sprue, which I failed to see as cultures were made and sent in by colleagues. All were negative for monilia. (6) Six cases with good histories of sprue awaiting confirmation by cultures. The preliminary plate cultures were mature at the time of my leaving San Juan. All seem to be of the type to which the new species belongs.

Twenty-five, therefore, of the 82 cases in this group yielded monilia on culture, but only 14 belonged to the new species, a percentage of 17 for the new species.

The third group consists of 66 cases. No one of these presented any symptoms of sprue, and many were apparently healthy in all respects. Four yielded monilia; two positive for the new species, the other two being entirely at variance therewith. The rest were negative for monilia, giving a percentage of three in this group for the new species. Animal experimentation will be detailed when completed.

The laboratory study of sprue has been limited to the working out of cultures, and this, naturally, has consumed much time, especially when one considers that all of the steps from the making of media, to titration, from collection of pathological specimens, to their cutting, mounting and staining, has with negligible exceptions, been done personally by the writer. Nevertheless, a few remarks may be made on the subject of animal experimentation.

Small laboratory animals are susceptible to inoculation by the new species, usually dying of a general mycosis in a few days if the monilia has not had its virulence weakened by age or too frequent transplanting. A large Belgian hare received a few drops of a ten-day culture of the monilia, recovered from the patient mentioned in the forepart of this paper, by hypodermic injection into the muscles of the tongue. Death occurred from general mycosis in seventy-five hours, and the necropsy cultures were made from liver, spleen, kidney, lung, heart's blood, and the muscles of the tongue. These cultures resulted directly pure for the new species in twenty-four hours. An interesting side-light is thrown by the morbid anatomy of this hare upon the statement of most writers who have had the good fortune to autopsy cases of sprue, as the mucous membrane of the bowel was found to be coated with a white, grumous layer. Owing to the leaking of the syringe, the animal had received by the mouth from 1 to 2 grams of the culture, and upon examining the stomach and small bowel they were found heavily lined with a white, creamy coating, examination of which demonstrated the immense preponderance of yeasts. To this it should be added that this animal, distinct from rats and guinea-pigs intraperitoneally injected, had a sharp diarrhea and an enormous production of gas before death.

Intraperitoneally, two white rats were injected, one with a glucose bouillon culture of the new species recovered from another American, who like the first died of the disease; the other with a similar culture from the daughter of a physician dangerously ill of sprue in the stage of marasmic toxemia. Both animals died of general mycosis, and from both, pure cultures were directly recovered from all the principal organs.

A hare which had proved himself resistant to the intraperitoneal injection of an old culture of the monilia, which promptly killed the first animal, received in the tissues of the ear 4 grams of a bouillon culture, and three weeks later it was found that the entire organ was the seat of a "blastomycotic" ulcer.

Feeding experiments, however, have been disappointing, although not yet persistently and systematically worked out. A guinea-pig of about 1000 grams was fed the new species in pure culture mixed with malted milk, it having been previously fed throughout a period of ten days with malted milk alone. Diarrhea and gaseous distention were produced, and after three weeks the animal died. The histopathological picture has not been worked out, but cultures from the organs were negative, save from mouth and stomach, which were positive for the new species and from the spleen, which gave a culture apparently unlike the new species.

A monkey similarly fed, became weak, morose, and emaciated, with sharp diarrhea, and the predominating organism in his stool is a yeast which in culture proved to be the new species of monilia.

In all feeding experiments, one should bear in mind that we are dealing with an organism of confessedly low virulence, and much patient and careful work must be done to elicit results worth citing as confirmatory.

The original technic of Wassermann was applied to the complement-fixation test for cases of sprue by Gonzalez Martinez, of our Institute of Tropical Medicine, just as I was leaving the island for the United States. I selected three strains of the new species from among my cases, and an antigen was prepared from these. Twelve cases not sprue were negative, and four clinically and mycologically sprue were positive. It is interesting to add that since that time all cases not sprue, and awaiting the Wassermann reaction for syphilis, are subjected to the complement-fixation test for sprue and are so far all negative.

Monilia, Species Undetermined. The organism is a typical monilia reproducing by side-buds and terminal conidia from specialized hyphæ, as well as by budding from yeast forms. Ascospores are never seen, but chlamydospore-like bodies are frequent, especially in older cultures. The yeast is round, from 2 to 7 microns in diameter, averaging from 3 to 4, with clear, clean-cut outline, usually containing a relatively large refractile body, and a much larger, faintly outlined vacuole. Tendency to mycelial formation is seen by the round yeasts enlarging and becoming oval. As the yeasts become larger, many active, highly refractive bodies of the size of a staphylococcus race incessantly about within the organism, reaching their largest number and greatest size in the chlamydospore-like, thick-shelled forms and frequently passing out into the fluid medium in which they grow, thus confusing the novice into believing that a contaminating coccus may complicate his apparently pure culture.

The mycelium is well developed, usually very abundant and presenting sparsely branching hyphæ, sometimes over a 1000 micra long which consist of articles from 10 to 60 micra long by 1.5 micra broad, the usual length being 15 micra. These hyphæ are of two distinct varieties; thin, often granular and 1 to 1.5 micra wide, and thick, often clear and 2.25 to 3 or 4 micra wide. The latter variety, at times without apparent structure interiorly, is more frequently punctuated at regular intervals by the highly refractile bodies described in the round and oval yeasts. These are from ½ to 2 micra in diameter and give a brilliant beaded appearance to the article. They stain as for chromatin by Giemsa. At times with the refractile bodies, at times without them, articles are seen frequently to have rectangular vacuoles of the same refractive index as though seen in the larger yeasts, thus dividing the article as it were into compartments and giving the hyphæ the appearance of a bamboo pole sawn longitudinally. In old culture many large yeasts are seen of 10 to 13 micra diameter as also involution forms of bizarre and clumsy outline, empty, collapsed chlamydospore-like bodies and heavy shelled prickle cells faintly suggesting the ova of ascaris lumbricoides.

Staining Reactions. The best class of stains for this organism belongs to the Romanowsky series. I personally prefer staining overnight in a weak Giemsa as by it the nuclear elements come out beautifully. The only satisfactory stain I have yet found for the outer shell of the mycelial threads is by Bodin's Victoria blue method. For staining in tissues there are only two methods that can be recommended and they are both of the highest excellence. The first is Weigert's fibrin method giving fine contrast by Gram's application. The second is Bodin's Victoria blue method. This may be summarized as follows: (1) Paraffin sections of mercuric chloride, absolute alcohol or formalin fixed tissue sections not over 5 micra; (2) after usual preparation for staining immerse for five minutes in a 1 per cent. erythrosin, aqueous solution. Wash well; (3) twenty-four hours in equal parts of a saturated alcoholic solution of Victoria blue and distilled water; (4) thorough washing in water and Weigert's stronger Gram solution for five minutes; (5) thorough drying and differentiation in aniline oil and xylol, equal parts; (6) thorough washing and clearing in xylol; (7) mount in balsam.

CULTURAL PECULIARITIES. The first labor was that of finding a specific medium. That one has been found in Sabouraud's glucose agar, 4 per cent. +2, is evident to anyone who cares to try it. As far as these yeasts are concerned it is ideal, as bacterial growth is efficiently inhibited even in strokes from feces and agar plates, the monilia standing out with unfailing precision as moist, white colonies of sharply contoured lines.

In culture from the tongue, a section lifter is sterilized in the flame and the borders and tip are gently scraped, the grumous material being spread upon a Sabouraud glucose agar slant by means of a sterile platinum loop. Twenty-four to forty-eight hours is all that is usually needed to bring out a monilia which is plated by the familiar three-plate method, and is easily recovered in another twenty-four to forty-eight hours in pure culture. For feces the Sabouraud agar is poured into a Petri dish, allowed to cool and harden, and is infected by parallel strokes. Suspicious colonies are then plated by the three-plate method. These methods were strictly observed in all cultures except that two, instead of three plates were frequently used.

The following media were employed in studying the species under consideration: Plain agar, glucose-, maltose-, levulose-, saccharose-, galactose-, lactose-, mannite-, dextrin-, erythrite-, raffinose-, dulcite-, isodulcite-, inulin-, and nutrose-agars. Loeffler's blood-serum mixture and plain blood serum; potato, plain and glycerinized; carrot, plain and glycerinized; plain gelatin, 20 per cent. +1;

plain and litmus milk; beer wort; Dunham's peptone solution; ox bile; plain bouillon, sugar-free bouillon; glucose-, maltose-, levulose-, saccharose-, lactose-, and mannite-, bouillons at 2 per cent. +1 and galactose-, dulcite-, dextrin-, raffinose-, arabinose-, inulin-, erythrite-, amygdalin-, asparagin and isodulcite at 1 per cent. +1.

The first four strains and several others later in the series were sown in all of these media and carefully checked upon as follows:

All cultures were run for at least two weeks and daily notes taken of each before deductions were made. Before final conclusions were reached the purity of the culture was tested. Solid media were allowed to run several months, especially gelatin cultures. All media were carefully titrated, as a rule to +1 by the rules of standardization of media recommended by the Bacteriological Committee of the American Public Health Association. Incubation was practiced at 33° to 35° without rubber tops to the tubes, these conditions being apparently most favorable to the growth of this monilia.

For fermentation tests, each culture in any sugar medium consisted of a fermentation tube, its control tube for final titration, and a litmus tube and its control to demonstrate daily progress in changing reactions. Incidentally it may be remarked that without titration by some such standardizing method as the one named above before sowing and at the close of the fermentation test, conclusions are greatly invalidated, as important and delicate reactions are quite missed. All sugar media were sterilized at the temperature of flowing steam for from ten to fifteen minutes on each of three successive days. Autoclaving splits the sugars. At the close of the period required for a complete fermentation test, the uninoculated media, which had been incubated along with the rest, was first titrated; then the inoculated media. Titration was performed in each case both hot and cold and the results recorded. The varying daily gas production was recorded as was the daily reaction in the corresponding litmus bouillon.

The monilia in question was found to prefer an acid, although it will grow well in alkaline media. Its adaptability is further shown in that on every medium tried it grew without difficulty, but it flourishes most luxuriantly on glucose, levulose, maltose, saccharose, galactose, and carrot.

The characteristics of the organism are best elicited by Sabouraud's glucose agar, carrot, blood serum, plain gelatin, litmus milk, and by fermentation tests in glucose, levulose, maltose, and saccharose bouillon (2 per cent. +1) and galactose bouillon 1 per cent. +1.

On Sabouraud's agar in from twenty-four to forty-eight hours a clean-cut, round, hemispherical, smooth, creamy white, moist, refractive colony is produced of the consistence of thick cream.

Small colonies are very beautiful under the lower power seeming to be like silvered mosaic. Later they tend to become acuminated in the centre and rapidly run together to form a thick cream all over the agar. They give off a yeasty smell and remind me of some Porto Rican bread and the stools of my cases. A young culture on solid media is not given to the production of mycelium but in the water of condensation it is abundant. Later the smooth creamy layer in some media, often apparently due to a mere bagatelle of half a per cent's difference in acidity of the original media, becomes knarled and twisted like a bunch of worms or the roots of a vine—or even like a delicate honeycomb.

The growth on carrot is distinguished by its tendency to rise high and stick rather closely to the line of plant, giving the appearance of heavy bits of raised embroidery. On blood serum a fine, not raised, at times almost invisible layer is made out. No liquefaction nor decolorization takes place. The growth in gelatin is remarkably faithful to type. It does not liquefy the media, stabs showing a limited round growth on the surface and fine hair-like lateral shoots all the way down to the lower extremity giving the appearance of a test-tube cleaning brush.

Milk is not coagulated and litmus milk grows steadily more and more alkaline. There is no period of acidity nor decolorization.

In discussing the sugar tests I shall have to take issue with the eminent authors whose versatility has enabled us to make use of these valuable but much over-rated means of differentiating species. Whether these gentlemen used our exact American methods of titration is open to speculation. They do not say that they did but I suspect that they did not. Had they done so perhaps Castellani and Chalmers would not offer such a bewildering series of "species" of monilia to the interested reader.

Such "species" as are to be depended upon not to produce gas when they are supposed to produce acid alone in a certain sugar bouillon, especially when they furiously ferment glucose, maltose and levulose, do not seem to me good. For one thing stands out quite clearly in these sugar tests: If a monilia produces acid, it is likely to produce gas, sooner or later. I have sown strain IV on one occasion and produced acid and gas in glucose, maltose and levulose; acid alone in saccharose and galactose. Two weeks later I have sown the same monilia, not from the culture on sugar media, possibly by that time educated to ferment sugars, but from the original source of the first culture. The result of this re-sowing was gas and acid in saccharose and galactose, as well as in the first three.

The species must not therefore be lightly made on sugar tests alone, when solid media, morphology and hanging drop specimens, not to mention inoculation results in animals, complement fixation tests, etc., speak for unity. In general, however, sugar tests are a wonderful help if one will only remember that a lively acid and gas producer in glucose, levulose and maltose will often do likewise in saccharose and galactose.

The species under consideration brings about a reaction tending toward alkalinity in all other sugar-media, with the possible exception that mannite and dextrin are apt to remain unchanged. Plain and sugar-free bouillon lose also in acidity. The characteristic of this monilia in bouillon is to leave the media clear, even after very long growth, with a more or less abundant sediment at the bottom of the tube. The growth at the surface varies, being almost nil if the organism does not grow vigorously in the particular media, very heavy if it does. Heavy growths at the surface produce a pellicle with a thick collar at the circumference which in the process of evaporation of the liquid is drawn out into a belt around the inside of the tube. Later this pellicle falls to the bottom and a new one takes its place. The superficial growth is more apt to have a predominance of mycelium, the sediment an excess of yeasts.

CONCLUSIONS. Bahr's evidence in favor of regarding sprue as a "blastomycotic" infection is as follows:

1. Yeast cells and mycelial elements are found intracellulary in scrapings of the tongue lesions at an early stage of the disease, but cannot be found at a later stage in scrapings of the same structure when inflammatory symptoms have subsided.

2. Yeasts are the only organisms found in the deep layers of the tongue in microscopic sections; the evidence that this infection is not one of recent date receives support from the chronic inflammatory changes in the corium of the papillæ, and from the presence of Russell's bodies in this situation.

3. The desquamation of the epithelial cells, accompanied by subacute inflammation of the tongue and of the esophagus, are changes such as would be expected from a study of the mode of growth of the thrush fungus and of its low order of virulence.

4. A general infection of the intestinal mucus with yeasts was found in sprue post-mortems, but no such a general infection in 26 cases of other chronic wasting diarrheas.

5. The stools of sprue, their frothy and gaseous character, are such as one would expect in a blastomycotic infection of the intestinal canal.

6. The relapsing nature, the chronicity and latency of the disease, are compatible with what is known of the life history of the blastomyces, their periods of attenuated growth and powers of sudden recrudescence.

7. There is no evidence in favor of regarding the sprue yeast fungus as being otherwise than identical with the thrush fungus (Monilia albicans), an organism possessing a very low pathogenic power, but it is possible that under certain conditions, as for instance

in the tropics, this power may be greatly augmented. In support of this view I may add that it is a well-recognized fact that there are numerous varieties of yeasts employed in brewing beer and in making wine, and the predominance of one variety in certain districts imparts to the local wine its characteristic flavor, which, though differing widely from each other in their powers of growth and fermentation, yet resemble each other minutely in their morphological and cultural character. May it not be that their pathogenic as well as their other properties, are capable of being influenced by local conditions?

8. Wasting and anemia, both symptoms of sprue, can be produced by continuous intravenous injections of small doses of broth cultures of a pathogenic yeast; moreover, a degeneration of the hepatic capillary endothelium, apparently similar to that found in the sprue spleen, may be produced in these animals by the same means.

9. Diarrhea, atrophy of the lingual papillæ as in sprue, digestive disturbance, and an aphthous ulceration of the mouth are commonly found in infants, the subjects of thrush infections in temperate zones.

10. It is possible that obscure diseases of the alimentary canal in children in temperate zones, such as Gee's celiac diarrhea, are of the same nature as sprue in adults in the tropics. A hypothesis of this sort would explain the occurrence of sporadic cases of sprue in temperate zones.

11. The local affection of different portions of the digestive tract with this fungus would best explain the varying clinical manifestations of sprue.

12. To maintain such a hypothesis it is necessary to stipulate for a third factor, a predisposing cause, which may exist in the local tropical climatic conditions, which favor a more precocious and luxuriant growth of all fungi, a matter of common observation to all laboratory workers in the tropics.

I am able to fully corroborate Bahr's evidence in all save human necropsy findings, as yet denied me, and with the exception of his statement that the sprue yeast fungus bears no evidence of being otherwise than identical with monilia albicans. In this matter we are not in accord as far as it may apply to Porto Rico where I have described a species, not *monilia albicans,* present in 100 per cent. of my cases of clinically positive sprue. In addition to this I have isolated this new species from the centre of a loaf of bread from an endemic focus in Porto Rico.

I therefore offer the following tentative conclusions drawn from the work as studied in Porto Rico and described in the body of this paper and from the accepted facts presented by authors regarding the human histo-pathology.

CONCLUSIONS. (*a*) *Clinical:*

1. Sprue is usually a mild disease with a veiled picture in which intestinal fermentation is usually present, a tendency to spontaneous cure and a ready submissiveness to a non-carbohydrate diet.
2. Tongue lesions are often clinically and histo-pathologically indistinguishable from ordinary thrush, a disease due as a rule to monilia albicans.
3. Clinically and histo-pathologically the picture of the tongue is projected on through stomach to intestine.
4. Chronic intoxication supervenes after well-developed sprue, and the liver atrophies without cirrhotic changes, secondary anemia making its appearance.
5. The intestinal lesions produce large, acid, frothy, white stools with excessive gas production, and full of yeasts. The character of these stools does not warrant the belief that serious ulceration takes place.
6. There is a tendency to chronicity and to periods of latency in which decided betterment or apparent cure may take place.
7. Drugs are of little avail save when used symptomatically for definite clinical crises and no specific has yet been found.

(*b*) *Epidemiological:*

1. Sprue is a disease of towns and cities where bread is a staple food.
2. Sprue is apparently rare in the country districts where bread is not at least a daily food and where often it is eaten only at long intervals.
3. Family endemics are noticeable.
4. There seems to be a racial predisposition to sprue in persons of northern birth.

(*c*) *Biological:*

1. A monilia, not heretofore described, and of undetermined species is apparently constantly found in cultures from the inflamed tongue or feces of persons suffering from sprue in Porto Rico.
2. This monilia has been found in the centre of a cooked loaf of bread baked in an endemic zone.
3. This monilia has been found in certain cases of fermentative disturbance of the intestine in which the complete picture of sprue is not developed.
4. The monilia is found in only 3 per cent. of persons, apparently entirely healthy or, at least, free from any gastro-intestinal disturbance.
5. The complement fixation test is positive for all of the reduced number of cases of complete sprue in which it has thus far been applied and negative for several times that number of persons without sprue.

6. This monilia is not only productive of mycotic septicemia in small laboratory animals injected with virulent culture but will produce severe and intractable mycotic ulcers in their tissues when they are relatively immunized to the extent of preventing a mycotic septicemia.

THE OCCURRENCE OF SPRUE IN THE UNITED STATES.[1]

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Tropical sprue, or psilosis, was probably first referred to in American literature in the writings of Dr. John Brickell,[2] a Dublin physician, who was an emissary of the Crown to the Cherokee Indians early in the eighteenth century. In his report he discusses the diseases of the colony of North Carolina, and in addition to yaws he mentions "white flux," which, in all probability, was the disease described in 1776 by Hillary, in Barbadoes, as sprue. The identity of this West Indian sprue was never questioned by Sir Patrick Manson,[3] though Carnegie Brown[4] still contends that true sprue is limited in its distribution to tropical and subtropical eastern Asia. Fortunately for us many of our medical men, especially of the Army Medical Corps, became familiar with true sprue in the Philippines, and not only brought back with them this intimate acquaintance, but were able to identify the disease known as sprue in Porto Rico as true sprue of the East. In recent years many observers have suspected that sprue existed in the United States, but only in the last decade has anyone had the temerity to actually make the diagnosis except in cases invalided from the tropics. The return of missionaries from China and Ceylon suffering from sprue has given us many opportunities to become familiar with true Eastern sprue and to compare it with the milder type of sprue in the Southern States.

In 1905 St. J. B. Graham,[5] of Savannah, reported four cases of sprue which had originated in Georgia. This observation was based on experience in the Philippines, and the correctness of the diagnosis can hardly be questioned.

In 1907 H. F. Harris,[6] of Atlanta, reported a number of cases of sprue. Later in that same year Searcy, of Alabama, reported

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[1] Presented at the meeting of the Association of American Physicians, in Washington, May 13, 1915.

[2] The Natural History of North Carolina, Dublin, 1737. Reprinted by the State Library of North Carolina.

[3] Tropical Diseases.

[4] Sprue, William Wood & Co., New York. 1908.

[5] Georgia Practitioner, August 15, 1905, xi.

[6] Tropical Sprue, Report of the Georgia State Board of Health, 1907.